

Malaria control in India: A national perspective in a regional and global fight to eliminate malaria

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ABSTRACT

Since the declaration of the vision of malaria eradication in 2007, the overall burden of malaria has been reduced substantially in many countries in the endemic world. This progress has, however, recently slowed worldwide and even an increase of morbidity and mortality has been observed in some regions. That reality has led to reflection on the strategy for malaria elimination, noting that focusing only on low transmission sites has competed with the efforts in countries that still have foci with high malaria burdens. This opinion piece outlines the collaboration of the ICMR-National Institute of Malaria Research (ICMR–NIMR) and other partner Institutions in India with the WorldWide Antimalarial Resistance Network (WWARN), one part of a global effort to manage the spread of *Plasmodium falciparum* parasites associated with antimalarial resistance.

Key words India; malaria; malnutrition; network; resistance

INTRODUCTION

Since the declaration of the vision of malaria eradication in 2007, the overall burden of malaria has been reduced substantially in many countries in the endemic world. This progress has, however, recently slowed worldwide and even an increase of morbidity and mortality has been observed in some regions¹. That reality has led to reflection on the strategy for malaria elimination, noting that focusing only on low transmission sites has competed with the efforts in countries that still have foci with high malaria burdens²⁻³.

India has the largest population at risk from malaria in a single country, with citizens living in extremely varied geographic and ecological areas⁴. Moreover, malaria manifests itself in a variety of forms such as tribal malaria, desert malaria, urban malaria and these require different approaches in management or elimination⁵⁻⁶. In addition, the diversity of the vectors and behaviour varies enormously within the country, further complicating strategies to control the disease. The growing urban development, laying of rail tracks and building activities also adds to the problem of vector control, increasing the risk of transmission in places that were previously malaria-free⁷⁻⁸. As a result of all these factors, the malaria burden has been historically among the highest and most complex in the world.

However, among the high burden countries, India stands out as it has continued to reduce malaria incidence

even as overall progress has levelled off. By 2017, malaria cases had been reduced by 24% in the country as a whole compared to the case burden in 2016^{2,9}. In 2015, India increased investment and scaled-up malaria control efforts nationally and committed malaria elimination by 2030.

Currently, areas of high malaria burden are concentrated in the East and Northeast of the country; six states contribute 75% of the reported cases (Fig. 1). An innovative collaborative project of the state and local malaria programmes, the ICMR-National Institute of Malaria Research (ICMR-NIMR) and the Medicines for Malaria Venture (MMV) has been focused on approaches to standardize and improve malaria diagnosis and treatment in some of these remaining foci. An interim report demonstrates that these changes have already had a significant impact on key indicators¹⁰, and a broader consortium has just been launched to respond appropriately to this interim data¹¹.

However, countries that have been certified free of locally transmitted malaria still face the challenge of importation of malaria from neighbouring, or even distant regions where malaria is endemic¹²⁻¹³. India has particular challenges. It shares a long border with Myanmar where *Plasmodium falciparum* parasites with reduced susceptibility to artemisinins are becoming predominant¹⁴⁻¹⁷. International human movements from the rest of SE Asia can also lead to the importation of artemisinin resistant *falciparum* parasites¹⁸. There is a recent report of patients carrying artemisinin resistant

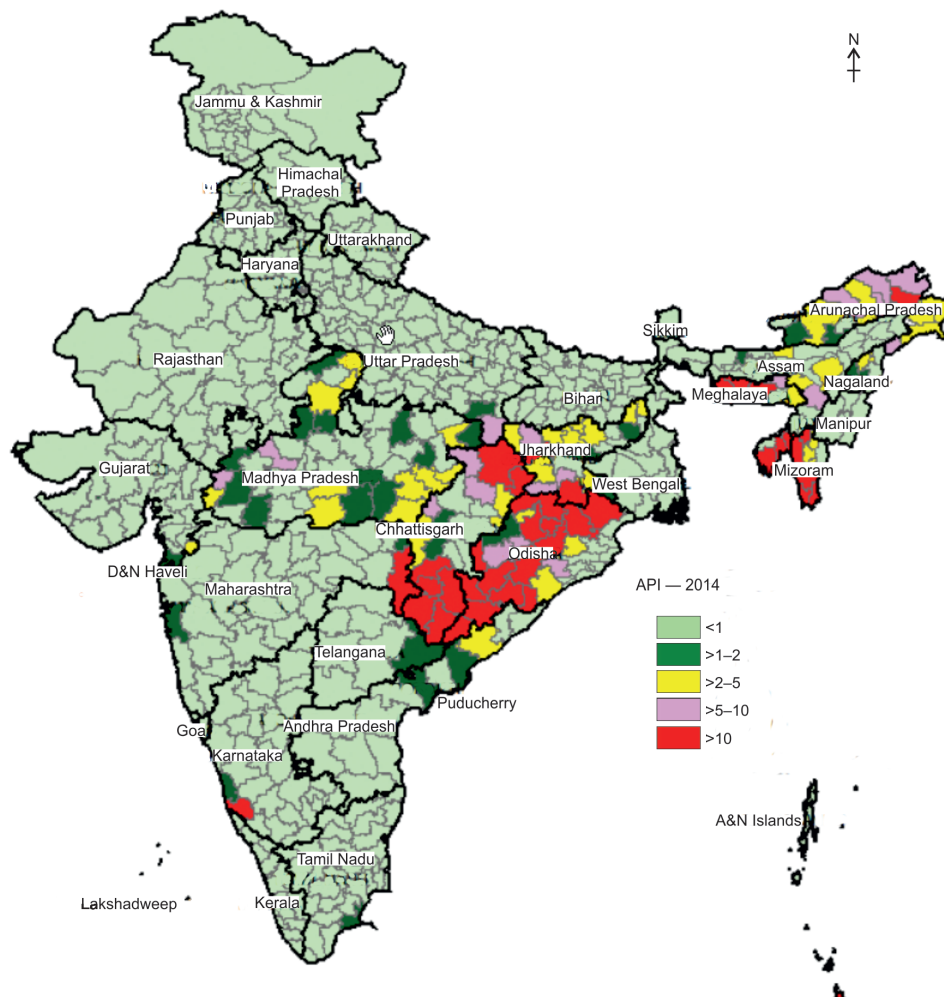


Fig. 1: Map of transmission intensity from Indian National Malaria Elimination Framework (reproduced with permission of ICMR-NIMR).

parasites into India from Southeast Asia^{19–20}. Although some concerns about the strength of the evidence have been raised²¹, such events may compromise the efficacy of the artemisinin combination therapies (ACTs) that are the foundation of efficacious malaria treatment in India and worldwide¹⁸. Malnutrition in children is highly prevalent in some parts of India and often common in the poorest regions where transmission of malaria is the highest. This co-morbidity raises specific issues of suboptimal dosage of antimalarials associated to poor bioavailability of the drug, which over the time, could facilitate selection of resistant parasites.

Furthermore, emphasis on elimination often focuses only on *P. falciparum*, but in Asia, *P. vivax* is a major part of the malaria burden (37% in India)¹. The prolonged period during which some individuals carry *P. vivax* allows them to carry infections far from their geographic source and long after the time of their initial infection. Thus, elimination of malaria must include radical cure of

P. vivax infections.

These internal and external challenges dictate that India's plans have included attention to regional and worldwide elimination activities. India's active participation in both the WHO/SEARO and, since 2015, in the Asia Pacific Malaria Elimination Network (APMEN) have provided a solid foundation for regional collaborations. In addition, Indian scientists have been a part of the planning and activities of the WorldWide Antimalarial Resistance Network (WWARN) since its inception in 2009. WWARN is a collaborative platform generating innovative resources and reliable evidence to inform the malaria community on the factors affecting the efficacy of antimalarial medicines and is part of the Infectious Diseases Data Observatory (IDDO). The Indian Council of Medical Research (ICMR) and the National Institute of Malaria Research have been the key members of the WWARN Board (Prof. Nirmal Kumar Ganguly—Former Director General of ICMR); Scientific Advisory

Committee (Dr Neena Valecha—Former Director of NIMR); and its independent Data Access Committee (Dr Anupkumar R. Anvikar—Scientist ‘F’ of NIMR) who advise on decisions on access to malaria datasets in the WWARN repository.

Furthermore, NIMR has participated in WWARN efforts by sharing data from a number of studies conducted by the Institute which were used subsequently for conducting individual patient data (IPD) meta-analyses^{22–25}. To date, these data sets have been used in 9 IPD meta-analyses, 4 that are currently in progress and 5 that have already been published^{14, 26–29}. These meta-analyses have contributed to a better definition of the impact of chloroquine dose and primaquine for the treatment of *P. vivax*²⁹. In collaboration with data contributed by colleagues from Africa, Asia and South America, the Indian data have also contributed to enhanced understanding of the efficacy of ACTs in these disparate locations. In particular, large harmonised datasets have tracked the extent of poor response to artemisinins¹⁴, examined the role of ACTs on parasite transmission²⁸ and provided the statistical power to identify vulnerable subgroups of patients, who are at increased risk of clinical failure after treatment with particular ACTs^{26–27}.

Along with NIMR, WWARN is a member of the Tracking Resistance to Artemisinins Collaboration (TRAC) led by the Mahidol-Oxford Tropical Medicine Research Unit. The initial TRAC studies first confirmed the presence of artemisinin-resistant parasites in Myanmar and other countries in the Greater Mekong Sub-region outside of Cambodia. These were followed by the TRAC2 trials focused on identifying effective and safe triple artemisinin-based combination treatments for infections with multi-drug resistant parasites. As for the TRAC studies, WWARN has also provided quality assurance and specimen management support to surveys being conducted by the St. John’s Research Institute in Bengaluru to assess the prevalence of genetic markers of drug resistance in remote forested areas of southern Odisha. Some of the highest malaria burden sites in India are in Odisha, and may make this region especially vulnerable to artemisinin resistance spreading over the border from Myanmar. All the available data on the prevalence of validated molecular markers associated with antimalarial resistance published in literature can be downloaded from the WWARN surveyors (<https://www.wwarn.org/tracking-resistance>). These interactive maps visualise the dynamic and spatial distribution of parasite resistance to antimalarials used in the region. The maps also illustrate that there are some gaps of up-to-

date information on the distribution of those markers in India; filling these gaps could improve knowledge easily accessible to stakeholders to guide their surveillance efforts.

The spatial and clinical heterogeneity of both *P. falciparum* and *P. vivax* in the Indian subcontinent engenders similar challenges to those encountered by global WWARN collaborations. In response, WWARN has developed and adapted tools to probe new questions that now need to be solved by the malaria community (<https://www.wwarn.org/tools-resources>). How can the effect of artemisinin on clearance of parasites be measured most reproducibly?^{30–31} How can laboratory-based assays be used to establish the response of parasites to drug challenge in the laboratory?³² What is the most effective way to treat the relapses that often follow initial *P. vivax* infections?³³ What is the relationship of the drug concentration in patient blood to parasite clearance and drug efficacy?^{34–36}.

The interim report of the NIMR collaborative programme designed to optimize treatment efficacy in the high burden regions of the Central and Northeastern regions of India¹⁰ certainly applies many such tools, and illustrates both the successes and remaining challenges that India now faces. The recognition that far better control of clinical malaria in high transmission sites must be addressed in parallel with efforts to eliminate importation of symptomatic and asymptomatic patients when transmission is low has sharpened the challenges for the malaria community^{2–3}. WWARN looks forward to continued productive collaboration with the NIMR both within India and in regional and global studies to address the issues facing the global malaria community.

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